Paget Disease of the Breast: A Rare, Often Misdiagnosed Malignancy

By Amelia Scholtz

A small, scaling rash around the nipple may not be just another case of eczema or dermatitis. Paget disease of the breast, a rare malignancy, is often mistaken for a benign dermatological condition. But Paget disease typically indicates underlying ductal carcinoma in situ or invasive breast cancer.

Clinical presentation

Paget disease of the breast is frequently misdiagnosed on initial presentation as eczema, which also may present as a rash affecting the nipple-areola complex. But Paget disease is seen in 1%–3% of new breast cancer cases. Paget disease of the breast is typically found in postmenopausal women 50–60 years old, although the disease also occurs in women of other ages and in men.

Unlike eczema and other benign skin conditions, Paget disease produces a firmness of the underlying tissue rather than a mere skin abnormality. In its initial stages, Paget disease typically appears as an erythematous, scaling lesion on the nipple. Patients may experience burning, pain, or itching at the lesion site. Flattening or retraction of the nipple, the spreading of the lesion to the areola, and a bloody discharge are associated with more advanced disease. Bilateral presentations of the disease are extremely rare.

Paget disease of the breast should also be distinguished from other types of malignant disease. Malignant melanoma may, like Paget lesions, have a scaly appearance. But unlike Paget disease of the breast, melanoma lesions do not bleed.

A photomicrograph of a biopsy specimen reveals Paget cells (arrows), which are larger than the surrounding keratinocytes and have prominent nuclei and moderate amounts of pale cytoplasm (hematoxylin and eosin stain, original magnification ×100).
Paget Disease of the Breast

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itch, or cause pain. Also, melanoma typically involves changes in skin pigmentation while Paget disease does not. Inflammatory breast cancer, like Paget lesions, may present as an erythematous abnormality on the skin. However, Michael Stauder, M.D., an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, said, “Inflammatory breast cancer is characterized by rapid onset of disease often accompanied by a palpable underlying mass.”

In 85%–88% of Paget disease cases, the nipple ulceration is accompanied by underlying ductal carcinoma in situ or invasive cancer, which may be multifocal. In the remaining cases, however, Paget disease is restricted to the skin, with no evidence of malignancy in the underlying breast—so-called pure Paget disease.

Pathogenesis

Perhaps owing to its rarity, Paget disease’s pathogenesis is still not well understood. “There are two theories to explain how the disease originates, and I don’t think they’re mutually exclusive,” said Henry Kuerer, M.D., a professor in the Department of Surgical Oncology.

On the one hand, the epidermotropic theory holds that Paget cells develop as part of an underlying breast malignancy. Some Paget cells then migrate via the lactiferous ducts into the breast epidermis. Similarities revealed by immunohistochemical staining between Paget cells and ductal epithelial cells support this theory. Moreover, Paget cells, which are large and contain pale cytoplasm and prominent nuclei, may differ significantly from other nipple tissue. One limitation of the epidermotropic theory is that it does not account for the development of Paget disease in the absence of an underlying tumor.

On the other hand, the transformation theory holds that epidermal keratinocytes become malignant and transform into Paget cells. The existence of cases in which underlying disease is absent or relatively distant from the skin lesion lends weight to this theory.

The identification in 1967 of what appear to be precursors to Paget cells—Toker cells—also supports the transformation theory. Defined by their clear cytoplasm, Toker cells have been observed across a spectrum from benign, to neoplastic, to atypical, to malignant. It is possible that the two theories describe alternative pathways through which Paget’s disease may develop; however, this is a continued source of controversy, and many researchers favor the epidermotropic theory. According to Savitri Krishnamurthy, M.D., a professor in the Department of Pathology, the epidermotropic theory accounts for more Paget disease cases than does the transformation theory. “We don’t know precisely how Paget disease of the breast develops,” she said, “but I think it’s more common to see ductal movement of malignant cells than it is to see this transformation of Toker cells.”

Diagnosis

Because of the initial clinical similarities between Paget disease and various benign conditions, patients commonly experience symptoms for several months before the histological diagnosis is made. The diagnostic workup for patients with symptoms resembling Paget disease typically begins with documentation of symptoms and a physical examination of both breasts. No risk factors specific to Paget disease have been identified to date, but clinicians consider risk factors for invasive breast cancer and ductal carcinoma in situ.

Patients with symptoms of Paget disease may be prescribed topical steroids at initial presentation to treat what appears to be a benign condition. “If the patient has developed scaling in the past week or so, it’s probably not appropriate to initially treat the problem as malignant,” Dr. Stauder said. “But if the abnormality has developed over months or years, there’s a need for more detailed investigation.”

If the lesion is not permanently resolved with steroid treatment, the patient should undergo bilateral mammography or ultrasonography. Inconclusive imaging results may necessitate a magnetic resonance imaging (MRI) study. Failure to find an underlying malignancy is one of the most serious problems that can occur in the diagnostic and treatment process. For this reason, Dr. Kuerer explained, “It’s critical that we have definitive, good imaging.”

When Paget disease is suspected, imaging is followed by biopsies of both the nipple lesion and any abnormalities or underlying malignancies located on imaging. In cases of suspected pure Paget disease, only the abnormal area of the nipple will be biopsied. Because MRI studies are sensitive but insufficiently specific, Dr. Kuerer said that MRI results should always be confirmed with a biopsy.

Although the sequence of initial
clinical presentation, then imaging, and finally pathological confirmation is the ideal for diagnosing Paget disease of the breast, the diagnosis is more often made by analysis of tissue obtained intraoperatively. Dr. Krishnamurthy said that most cases of Paget disease are identified after routine evaluation of the skin of the nipple-areola complex in patients who have undergone mastectomy for an underlying malignancy. In such cases, the patient may have undergone surgery for a tumor within the breast without Paget disease’s being suspected prior to pathological analysis.

Whether conducted on tissue obtained preoperatively or removed surgically, pathological analysis of Paget disease specimens typically reveals Paget cells scattered or in small groups in the nipple epidermis. Pathologists perform a detailed histopathological examination as well as ancillary histochemical and immunohistochemical staining to distinguish Paget cells from normal and malignant keratinocytes, melanoma cells, and Toker cells. For example, Paget cells and some Toker cells can stain positive for mucins, but keratinocytes and melanoma cells do not. The immunophenotype of Paget cells differs from Toker cells; Paget cells do not. The immunophenotype of Paget cells remains the standard treatment; these patients also undergo intraoperative sentinel lymph node biopsy. This biopsy is typically not performed during breast-conserving surgery unless there is also evidence of invasive cancer.

For many patients, the nipple-areola complex is important for sexual intimacy, and the effects of the complex’s resection on intimacy should be discussed with patients early in the treatment process. Peer-to-peer and individual counseling programs are an important source of support in this regard.

After surgery, most patients with underlying disease will undergo adjuvant radiation therapy, which is administered to the whole breast. An intraoperative finding of node-positive disease may necessitate adjuvant chemotherapy in addition to radiation. In a minority of patients with underlying disease, various factors may make adjuvant radiation therapy inadvisable. For example, Dr. Stauder suggested that a patient more than 70 years old with invasive carcinoma who has a small tumor and poor functional status would not be a good candidate for radiation therapy. Instead, if their underlying disease is hormone receptor positive, such patients may receive oral systemic therapy with hormone receptor antagonists such as tamoxifen and/or aromatase inhibitors such as anastrozole. Patients with pure Paget disease will rarely undergo radiation therapy but may receive oral systemic therapy if their disease is hormone receptor positive.

Prognosis and trends

For patients with underlying disease, the prognosis, like treatment, depends on the stage and type of the underlying disease. The largest study of Paget disease of the breast to date—a 2006 review of Surveillance, Epidemiology, and End Results data—found that women with Paget disease and underlying invasive breast cancer had a 15-year diseasespecific survival rate of 61%, whereas the rate was 94% for women with Paget disease with in situ carcinoma and 88% for those with pure Paget disease. Tumor size and lymph node status were found to be key determinants of disease-specific survival.

Because of the rarity of Paget disease of the breast and the fact that treatment is determined by the underlying disease, new developments in Paget disease—specific research and treatment are few. Research into the pathogenesis of Paget disease would help to deepen the understanding of the disease’s progression and allow for more precise selection of treatment regimens for individual patients. However, Dr. Stauder said that in the absence of Paget disease–specific data, “The existence of relevant equivalent data on ductal carcinoma in situ and invasive breast cancer still allows for prudent treatment planning.”

Indeed, there is reason for optimism: The 2006 study showed that from 1988 to 2002 the incidence of Paget disease with underlying invasive or in situ disease decreased and the incidence of pure Paget disease remained stable. Dr. Kuerer speculated that the increased use of screening mammography might account for the reduced incidence of Paget disease with underlying disease. He said, “I think there’s going to be a higher proportion of Paget disease cases involving only the nipple-areola complex—so-called pure Paget disease—because women are so knowledgeable about signs of potential breast disease that we’re catching breast cancer earlier.”

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Dr. Michael Stauder.............713-563-3623

FURTHER READING
New Partial-Breast Radiation Therapy Regimen Uses Protons

By Bryan Tutt

Whole- or partial-breast radiation therapy can reduce a patient’s chance of breast cancer recurrence after lumpectomy, but this benefit must be weighed against the risk of damage to healthy tissue.

A new partial-breast irradiation regimen employing protons shows promise as an effective adjuvant treatment that minimizes the radiation dose to healthy tissue.

Whole-breast irradiation, the standard of care, has a proven track record but may damage healthy breast tissue or, rarely, nearby organs such as the heart or lung. The currently used modalities for accelerated partial-breast irradiation target the region adjacent to the initial tumor and typically deliver treatment over a 1-week period. These modalities reduce but do not eliminate the radiation dose to healthy tissue.

The most common partial-breast irradiation modalities are three-dimensional (3D) conformal external-beam radiation and brachytherapy. “With 3D conformal therapy, about half of the breast receives half the dose,” said Eric A. Strom, M.D., a professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center. With brachytherapy, Dr. Strom added, the radiation sources, which are inserted near the tumor site via a needle or catheter and emit radiation in all directions, also affect healthy tissue as well as the tumor bed.

In contrast, proton therapy has virtually no scatter (radiation to tissue outside the treatment field) but presents a different problem. Protons release a relatively small radiation dose when they enter the body and move through tissue until they start to run out of energy. At the end of their energy range, protons suddenly release their remaining dose of ionizing radiation—the Bragg peak—with no scatter. “The problem is that to treat a tumor bed, you have to stack a lot of these Bragg peaks on top of one another at various depths,” Dr. Strom said. When the tumor bed is near the skin surface, as many breast tumors are, the same area of skin receives multiple small doses, which add up to a large cumulative entrance dose.

This high entrance dose caused minor burns and skin irritation in breast cancer patients in the early proton therapy studies, which were not done at MD Anderson. Because skin sparing is a benefit of both 3D conformal radiation therapy and brachytherapy, proton therapy has not been commonly used for breast cancer patients—until recently. A phase II clinical trial now under way at MD Anderson is testing the effect of multiple proton beams aimed at the tumor bed from different directions. “By spreading the skin dose over several adjacent areas, no one point gets a high dose,” said Dr. Strom, the study’s principal investigator.

Participants in the study are women who have undergone lumpectomy for ductal carcinoma in situ or stage I or II invasive adenocarcinoma of the breast. The inclusion and exclu-
Managing Dental Complications in Patients with Head and Neck Cancer

By Luanne Jorewicz

Dental complications in patients with head and neck cancer can be serious or even life-threatening if not managed effectively.

These dental issues most often result from radiation therapy, but surgery and chemotherapy also can cause or exacerbate dental and periodontal problems. Careful attention before, during, and after cancer treatment can minimize these complications.

Dental complications

Dry mouth (xerostomia) is a common side effect of radiation therapy for head and neck cancer. “Most patients receiving radiation treatment for head and neck cancer will have some level of dry mouth, particularly if major salivary glands are within the field of radiation,” said Mark Chambers, D.M.D., a professor in the Department of Head and Neck Surgery and chief of the Section of Oral Oncology and Maxillofacial Prosthodontics at The University of Texas MD Anderson Cancer Center. Unfortunately, xerostomia can become a chronic complication. Some chemotherapy drugs also may cause xerostomia.

By lowering the pH of saliva, xerostomia contributes to tooth decay, plaque buildup, and gum disease. Xerostomia also makes patients more susceptible to fungal infections, particularly candidiasis.

Radiation therapy also may cause blood flow to decrease in treated areas, and the lack of blood to the bone may lead to osteoradionecrosis, a serious and chronic complication. The bone becomes devitalized and develops abscesses, which often defy healing. In patients with osteoradionecrosis of the mandible or maxilla, the jaw’s inability to heal can cause complications if other dental problems necessitate tooth extraction. Jaw fractures, and the resultant tooth damage, also are not uncommon in patients with osteoradionecrosis.

In a study of osteoradionecrosis, Beth Beadle, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology, and her colleagues reviewed the Surveillance, Epidemiology, and End Results–Medicare database to see which side effects had been treated in Medicare recipients who received radiation therapy for head or neck cancer from 1999 to 2007. Of those 1,848 patients, 227 patients (16%) exhibited some degree of jaw complications, although only a small minority of these were severe.

Patients with any type of cancer may experience diminished wound-healing capability owing to immunosuppression from chemotherapy. As levels of white and red blood cells and platelets drop, tooth or gum infections can result in mucositis.

Preventing and managing dental complications

Dr. Beadle said that radiation oncologists meticulously plan their treatment fields to minimize damage to salivary glands and other sensitive areas. Even so, radiation to sensitive areas may be unavoidable when treating nearby tumors, and dental complications remain a major risk for patients receiving radiation to the head and neck.

To reduce the incidence and severity of dental complications, at MD Anderson dentistry is a core component of treatment plans for all patients with cancer in the head and neck region. Theresa Hofstede, D.D.S., an associate professor in the Department of Head and Neck Surgery, said that patients

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To learn more about the ongoing clinical trial of partial-breast irradiation with protons, visit www.clinicaltrials.org and select study No. 2009-0818.
Managing Dental Complications

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with head and neck cancer are evaluated for oral infections, gum issues, broken teeth, and unsalvageable or rotted teeth before, during, and after cancer treatment.

Preexisting tooth or gum issues or infections ideally are treated 1–2 weeks before cancer treatment begins. These preexisting conditions can lead to more dangerous complications if not resolved. For example, infections or pain may become serious enough to require a break in a patient’s cancer therapy. Infections also could lead to sepsis, which can be life-threatening to patients with compromised immune systems.

During radiation therapy, Dr. Hofstede and other faculty members in the Section of Oral Oncology and Maxillofacial Prosthodontics work closely with the radiation oncology team to address dental issues before they create even greater health risks for the patient. Patients with xerostomia are encouraged to keep their mouths clean to avoid dental caries and periodontal complications.

Repairing surgical damage

Patients whose tumors must be surgically removed sometimes lose a portion of the jawbone. To assist with the patient’s rehabilitation after surgery, Dr. Hofstede may develop a prosthesis, such as a maxillary obturator or a mandibular resection prosthesis, to restore chewing, swallowing, and speech. These prostheses are somewhat like dentures, but

they include a replacement for the missing jaw portion. The prosthesis may be held in place by hooks that fit around existing teeth and bones or may attach to dental implants.

IN BRIEF

NF-κB May Be Linked to Glioblastoma Treatment Resistance

NF-κB, a transcription factor associated with inflammation, and its signaling pathway may be key factors in glioblastoma aggressiveness and treatment resistance, according to new research conducted by an international group led by researchers at The University of Texas MD Anderson Cancer Center.

The research was part of an ongoing effort to identify the risk factors for and contributors to aggressiveness in glioblastoma. In this study, the researchers isolated two distinct subtypes of glioblastoma cells and showed that the more aggressive and radioresistant mesenchymal subtype of glioblastoma spontaneously converted into the less aggressive proneural subtype in cell cultures. The researchers also found that this conversion could be reversed by adding NF-κB activators to the culture medium.

Although it was previously known that cells could transition from the less aggressive proneural to the more aggressive mesenchymal subtype, the mechanism governing this transition was not known.

“The transition of tumor cells to a mesenchymal type, characterized by gene expression associated with invasion and new blood vessel formation, leads to radiation resistance,” said Erik Sulman, M.D., Ph.D., an assistant professor in the Department of Radiation Oncology and a co–senior author of the study’s report. The findings were published in September in the journal Cancer Cell.

When the researchers isolated glioblastoma cells from patients in attempts to further characterize the different types of glioblastoma cells, they found something surprising: many of the originally mesenchymal cells converted into proneural cells in cell cultures. This result was unexpected because glioblastoma almost never reverts to a less aggressive state in patients.

The unexpected findings led the team to investigate possible mechanisms for this reversion. The researchers treated proneural glioblastoma cells with tumor necrosis factor (TNF), a cytokine that causes NF-κB signaling, and the cell cultures reliably converted into the radiation-resistant mesenchymal subtype; this effect could be reliably reversed by blocking NF-κB signaling.

This finding showed that NF-κB signaling plays an important role in the typical transformation from proneural to mesenchymal cells. This result was unexpected because glioblastoma almost never reverts to a less aggressive state in patients.

The unexpected findings led the team to investigate possible mechanisms for this reversion. The researchers treated proneural glioblastoma cells with tumor necrosis factor α, a cytokine that causes NF-κB signaling, and the cell cultures reliably converted into the radiation-resistant mesenchymal subtype; this effect could be reliably reversed by blocking NF-κB signaling.

This finding showed that NF-κB signaling plays an important role in the typical transformation from proneural to mesenchymal cells. According to Dr. Sulman, “These results suggest that blocking the inflammatory response to make tumors more sensitive to standard radiation treatment may improve outcomes for glioblastoma patients.”
Health Benefits of Quitting Smoking
It’s never too late to quit, but sooner is better

By now, everyone knows that smoking is dangerous. But fewer people are aware that quitting smoking can significantly improve your health, no matter how old you are or how long you’ve smoked.

Hazards of smoking
According to the U.S. Centers for Disease Control and Prevention (CDC), smoking is responsible for almost one in every five deaths and causes the premature deaths of more than 440,000 people each year in the United States. The CDC estimates that adult male smokers lose an average of 13.2 years of life because of smoking and that female smokers lose 14.5 years.

Smoking is a leading cause of many cancers, including cancers of the lung, mouth, throat, kidney, bladder, pancreas, stomach, and cervix.

Smoking also can cause heart disease, stroke, chronic obstructive pulmonary disease (chronic bronchitis and emphysema), and asthma. In addition, smokers have higher risks than nonsmokers of hip fractures and cataracts.

Finally, pregnant women who smoke are more likely to miscarry or have babies with low birth weights. Babies with low birth weights are more likely to die as infants or have physical and learning problems.

Benefits of stopping
The good news is that quitting smoking has immediate positive health effects for smokers of any age, and these benefits may apply even to people who already suffer from smoking-related diseases.

You experience some of these effects the first day you quit. Your heart rate and blood pressure, which increase when you smoke, return to their normal levels after 20 minutes without smoking. Within 12 hours, the carbon monoxide level in your blood drops to normal, according to the U.S. Surgeon General.

Soon you are likely to notice that food tastes better, your sense of smell is returning to normal, and physical activities that once left you out of breath, such as climbing stairs or housework, no longer bother you.

Quitting smoking has positive effects on your appearance as well. Stained teeth get whiter, and the yellow tinge to your fingers and fingernails disappears. Also, the bad smell on your clothes and hair is no longer there.

As you continue to forgo smoking, the benefits to your health keep expanding. Within 2–3 months of quitting, your circulation improves, and your lung function increases. Your risk of having a heart attack begins to drop.

Women who stop smoking before pregnancy or during the first 4 months of their pregnancy reduce their risk of having a baby with low birth weight to the level of women who never smoked.

Your coughing decreases 1–9 months after you quit. Cilia, the tiny hair-like structures that move mucus out of the lungs, start to regain normal function, which cleans the lungs and reduces the risk of infection.

One year after you stop smoking, your risk of coronary heart disease is still higher than that of someone who never smoked, but the added risk is half that of someone who still smokes. Five years after quitting, your risks of cancer of the mouth, throat, and bladder are cut in half. Cervical cancer risk becomes the same as that of a lifelong nonsmoker 5 years after quitting. The risk of having a stroke is the same as a lifelong nonsmoker’s after only 2–5 tobacco-free years.

By 10 years, giving up tobacco has decreased your risk of cancers of the larynx (voice box) and pancreas. Your risk of dying from lung cancer is now about half that of a person who still smokes. At 15 years, your risk of coronary heart disease is the same as a lifelong nonsmoker’s.

No matter what age you stop smoking, there are health benefits. According to studies, smokers who quit around 30 years of age reduce their chances of dying prematurely from smoking-related diseases by more than 90% compared with people who continue to smoke. Smokers who quit when they are 50 years old reduce their risk of premature death by 50% compared with those who still smoke. Smokers who quit when they are 60 years or older also live longer than people the same age who continue to smoke.

If you smoke, quitting smoking is the single most important step you can take to improve your health and increase your chance of living a long, healthy life.

K. Sneyck

FOR MORE INFORMATION
• Talk to your physician
• Visit www.mdanderson.org
• Visit the CDC at www.cdc.gov/tobacco
• Call askMDAnderson at 877-632-6789
• Call MD Anderson’s Tobacco Treatment Program at 713-792-7848 or 866-245-0862
Managing Dental Complications

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“Most patients receiving radiation treatment for head and neck cancer will have some level of dry mouth, particularly if major salivary glands are within the field of radiation.”

– Dr. Mark Chambers

Because the patient will need to use this prosthesis for the rest of his or her life, Dr. Hofstede’s team will continue to work with the patient to ensure that any changes in status are addressed so that the patient can live as normal a life as possible.

Some patients who undergo newer reconstructive techniques with bone and tissue transfers receive dental implants that are permanently screwed into the reconstructed jaw. Dr. Hofstede said these osseointegrated implants “expand our ability to successfully rehabilitate our patients for a better quality of life.”

Continuing care

Like surgery, radiation therapy to the head and neck presents long-term challenges, even after a patient’s cancer has been successfully treated. As Dr. Chambers said, “Once radiation, always radiation challenges.” For this reason, he said he advises patients who have received such therapy to address dental issues promptly and thoroughly, as these issues can rapidly become health- or life-threatening. For example, while the average person might visit the dentist once a year, most current and former cancer patients are urged to visit their dentists at least twice a year; patients with chronic dental complications resulting from radiation to the head and neck region may need even more frequent appointments. Keeping the mouth clean, acid-free, and healthy can improve the overall health and quality of life for head and neck cancer survivors.

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FURTHER READING


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